REMARKS

Claims 1-3, 7, 9-10 and 15-18 are pending in the present application. Claims 1-3, 9-10 and 15-17 stand rejected. Claims 7 and 18 are objected to. Claim 9 is amended with support as described below. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made." No new matter is believed added.

I. Rejection under 35 U.S.C § 102 (b)

Claims 9-10 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Al-Hakim et al. The Office Action reiterates arguments from Paper No. 9, stating that Al-Hakim et al. teaches the construction and use of nucleic acid probes that feature an adduct of a basic macromolecule and biotin in which the macromolecule can be polyethyleneimine, in which the adduct can be cross-linked to a nucleic acid to form a nucleic acid hybridization probe and in which the hybridized probe can be detected by an avidin-enzyme label complex which binds to the biotinylated nucleic acid-PEI probe. Therefore, the Office Action asserts that Al-Hakim et al. does disclose a complex comprising a biotinylated nucleic acid-PEI/avidin-enzyme composition. Further, the Office Action asserts that failure of Al-Hakim et al. to disclose a PEI-avidin adduct is irrelevant as this limitation is not present in the claim as recited.

Claim 9 is amended herein to recite, "...wherein the polyethyleneimine is covalently linked to avidin." Support for the amendment of claim 9 can be found throughout the application as filed, but especially at page 14, line 9 to page 15, line 23 where the preparation of a nucleic acid-polyethyleneimine-avidin conjugate is described in detail, including the steps of: 1) covalently cross-linking PEI and avidin; 2) complexing nucleic acid to the covalently cross-linked PEI-avidin conjugate. Applicants respectfully submit that this additional limitation distinguishes amended claim 9 and dependent claim 10 from the cited art. Specifically, Al-Hakim et al. does not teach any nucleic

acid-polyethyleneimine-avidin complex, wherein the polyethyleneimine is covalently linked to avidin. In fact, the whole purpose of Al-Hakim et al. would be frustrated by a construct as recited in amended claim 9, because introducing a covalent linkage between avidin and polyethyleneimine would result in molecules wherein the nucleic acid would be covalently linked to the reporter enzyme (via the polyethyleneimine linker). As outlined in Al-Hakim et al., covalently linking a reporter enzyme to a nucleic acid gives rise to one of the specific problems of the prior art, the interference of the attached enzyme with hybridization, that Al-Hakim et al. were attempting to solve (see column 1, lines 24-33). Applicants respectfully submit that Al-Hakim et al. does not anticipate the invention as recited in amended claim 9.

II. Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-3 and 15-17 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one of skill in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. As stated in the Office Action, this is a new rejection.

The Office Action states that each of claims 1-3 and 15-17 is drawn towards a method for delivering a biologically active biomolecule to the surface of a cell wherein a first molecule is covalently attached to the surface of the cell to form a receptor, a biologically active molecule is complexed with a ligand for the first, covalently attached molecule, and the cell surface is contacted with the molecule-ligand complex. The Office Action further states that claims 1-3 comprise a further limitation, namely, the delivery of the biologically active molecule to the surface of the cell. These claims are alleged, by the Office Action, to literally encompass the attachment of any molecule to the surface of a cell of any type wherein the first molecule will specifically bind a ligand such that a biologically active molecule-ligand complex can be delivered specifically to the cell surface. Specifically, it is alleged that the claims encompass any active biomolecule, including peptides,

nucleic acids, lipids and carbohydrates complexed with a carrier molecule to which the ligand is complexed, and any possible "receptor/ligand" binding pair regardless of chemical structure.

It is further alleged that the only description provided in the specification for a "receptor"/ligand binding pair is where biotin has been covalently attached to the surface of a target cell to form a "receptor" for an avidin (or streptavidin)/biologically active molecule complex ligand. It is further alleged that the description of ligand/biologically active molecule complexes is limited to complexes wherein the ligand is complexed with PEI as well as with the biologically active molecule. It is further alleged that the only biologically active molecules for which there is significant description in the ligand/active molecule complex are nucleic acids and polypeptides. Most specifically, the Office Action states that "there is no significant description or relevant example in the specification for a ligand/biologically active molecule complex other than complexes comprising avidin (or streptavidin) complexed with PEI, and further complexed with either a polypeptide or a nucleic acid."

Due to the broad scope of the claims, specifically claims 1-3 and 15-17, specifically regarding the broad scope of the "receptor" attached to the surface of the target cell and the corresponding ligand/active molecule complex, the alleged lack of description for "receptor," ligand/active molecule combinations, and the different chemical/structural requirements for different "receptor" molecule/ligand/active molecule complexes, the Office Action alleges that one of skill in the art would not be able to envision a representative number of embodiments.

Moreover, the Office Action asserts, that even if one limited the present invention to those systems comprising biotin/avidin receptor/ligand pairs, one would still not be able to envision a representative number of embodiments wherein the active molecule is a molecule other than a nucleic acid or a peptide.

Applicants respectfully disagree with the Office Action's characterization of what is disclosed in the application as filed, what would be considered to be within the skill of one in the art, and what embodiments of the invention are reasonably conveyed to one of skill in the relevant art at the time the application was filed.

Specifically, in response to the Office Action's assertion that the only description provided for a "receptor"/ligand binding pair is that of biotin covalently attached to the surface of a target cell to form a "receptor" for an avidin (or streptavidin)/biologically active molecule complex ligand, Applicants submit that the specification as filed, and references cited therein, recite the use of specifically outlined receptor molecules, and types of receptors, which when covalently attached to the target cell surface may function as "receptors" for use with "ligands" in the practice of the invention. Such specifically outlined receptor molecules include: asialoglycoprotein receptors for use with asialoglycoproteins and/or galactosylated ligands (page 2, lines 23-24 and reference cited therein (Zanta et al., *Bioconjug. Chem.* 8: 839-844 (1997), attached as Exhibit A)); folate receptors and ligands comprising folate or folate analogs (page 2, lines 25-29 and reference cited therein (Dachs, *Oncol. Res.* 9: 313-325 (1997), attached as Exhibit B)); transferrin receptors and bioconjugates comprising transferrin (page 2, line 29 to page 3, line 2 and reference cited therein (Schwarzenberger et al., *J. Virol.* 71: 8563-8571(1997), attached as Exhibit C)); and cytokine receptors with cytokine (page 7, line 13), in addition to biotinylated species to act as receptors with bioconjugates comprising avidin or streptavidin. This art cited in the application and specifically incorporated by reference describes the use of a broad range of receptors to direct their corresponding ligands, and associated conjugates of the ligands, to cells bearing appropriate receptors. Further, Dachs et al. describes the use of ligands to epidermal growth factor receptor (EGF-R) and the receptor tyrosine kinase of the proto-oncogene c-*kit* to target delivery of agent to cells bearing these receptors. Still further, Applicants refer the Examiner's attention to the references cited in the specification wherein these receptors, or the types of molecules of which these receptors belong, are routinely manipulated by those of skill in the art, including covalently linking molecules to a cell

surface. These references include each of those cited in the above-indicated portions of the specification, including "Bioconjugate Techniques," by G.T. Hermanson, Academic Press, Inc. (1996), cited on page 6, lines 29-30. Particularly relevant portions of Bioconjugate Techniques are provided as Exhibits D-H. Exhibit D describes the avidin-biotin interaction (pages 570-571). Exhibit E describes biotinylation reagents and methodologies useful in making and practicing many aspects of the invention (pages 371-400). Exhibit F describes biotinylation techniques and methods for determining the level of biotinylation obtained (pages 590-592). Exhibit G describes the preparation of avidin or streptavidin conjugates (pages 575-584). Exhibit H provides a list of functional targets for the modification procedures described which includes amino acids, peptides and proteins (pages 3-26); sugars, polysaccharides and glycoproteins (pages 27-40); and nucleic acids and oligonucleotides (pages 40-56). Further, Exhibit H provides methods for creating specific functional groups not normally present in the unmodified species (pages 56-136). These teachings, read in combination with the teaching of the present invention, provide a broad basis of enablement for covalent linking of a variety of molecules to cell surfaces and use of those receptors for their known ligands.

In response to the Office Action's assertion that description in the application as filed is limited to ligand/biologically active molecule complexes wherein the ligand is complexed with PEI as well as with the biologically active molecule, Applicants submit that PEI-avidin is merely one possible option that a skilled practitioner may select from the many disclosed in the specification as filed. Other possibilities disclosed include ligands for asialoglycoprotein receptors, such as those comprising galactosylated polylysine or galactosylated polyethyleneimine (page 2, lines 23-25; page 7, line 12; and Zanta et al. (provided as Exhibit A) cited therein); folate ligands for folate receptors (page 2, lines 25-29; page 7, line 13; and Dachs et al. (provided as Exhibit B) cited therein); transferrin ligands for transferrin receptors (pages 2, line 29 to page 3, line 2; page 7, line 12; and Schwarzenberger et al. (provided as Exhibit C) cited therein); avidin (streptavidin) (page 7, lines 2-5); and cytokines, such as interleukin (IL)-3 (page 7, line 13). Therefore, Applicants submit that the

description in the application as filed is not limited to ligand/biologically active molecule complexes wherein the ligand is complexed with PEI as well as with the biologically active molecule.

In response to the Office Action's assertion that there is only significant description for nucleic acids and polypeptides as the biologically active molecules in the ligand/active molecule complex, Applicants submit that the application provides clear support for a much broader range of biologically active molecules than just nucleic acids and peptides. As filed, the specification provides clear support for what is intended by the term "biologically active molecule" and teaches that the meaning of the term is not limited to nucleic acids and polypeptides. See for example, page 5, lines 17-30, wherein the specification recites, "....a biologically active molecule is one or more molecules which can, upon entering a cell, affect cellular metabolism or other cellular activities. Proteins, enzymes, vitamins, vaccines, transcription factors, hormones, carbohydrates, lipids, and nucleic acids... ...are examples of biologically active molecules." Further, Applicants again direct the Examiner's attention to the previously cited examples of diverse molecules envisioned as components of the presented disclosed invention in combination with their receptors. Applicants submit that this is a sufficient number of representative examples to provide the claimed genus without undue experimentation. Applicants request removal of this basis of rejection.

In response to the Office Action's statement that "there is no significant description or relevant example in the specification for a ligand/biologically active molecule complex other than complexes comprising avidin (or streptavidin) complexed with PEI, and further complexed with either a polypeptide or a nucleic acid," Applicants submit that the application as filed provides significant description of numerous examples of ligand/biologically active molecules complexes, including galactosylated-PEI-DNA complexes (page 2, lines 23-25 and reference cited therein (Exhibit A)); folate analog-DNA complexes (page 2, lines 29 and reference cited therein (Exhibit B)); transferrin-polylysine-plasmid complexes (page 2, line 30 to page 3, line 2 and reference cited therein (Exhibit C)); cytokine-cytokine receptor complexes (page 7, line 13) and biotinylated

antibodies-avidin or streptavidin (page 7, lines 14-17). Applicants submit that the application as filed, as evidenced by the above cited portions, provides adequate description of a sufficient number of representative examples to support the claimed genus without undue experimentation. Applicants request removal of this basis of rejection.

Applicants respectfully disagree with the Examiner's assertion that because of the broad scope of the claims, specifically claims 1-3 and 15-17, more specifically regarding the broad scope of the "receptor" attached to the surface of the target cell and the corresponding ligand/active molecule complex, the alleged lack of description for "receptor," ligand/active molecule combinations, and the different chemical/structural requirements for different "receptor" molecule/ligand/active molecule complexes, one of skill in the art would not be able to envision a representative number of embodiments. Specifically, Applicants submit that for the reasons stated *supra*, there is not a lack of description for receptors or ligand/active molecule combinations. Further Applicants submit that the application as filed provides a sufficient number of representative examples to provide the claimed genus without undue experimentation as many of the recited receptor and ligand-active molecule complexes have been used by those of skill in the art for decades in other contexts (see for example, page 2, lines 25 to page 3, line 2) and as such would be recognized by those of skill in the art to be but representative examples of a larger group of molecules with which to make and practice the current invention.

Applicants further submit that the state of closely related arts was sufficiently well-developed to allow one of skill in the art to envision a larger number of embodiments of molecule/ligand/active molecule complexes than is specifically recited in the specification or in references cited therein. A review of the state of one related art, from 1979, indicates just how well-developed the principles and techniques underlying the practice of some embodiments of the present invention were at even that early date (Keusch, *Rev. Infect. Dis.* 1(3): 517-529(1979) (Exhibit I)). Specifically, Keusch describes the nature of interactions between pathogens and the cell surface of cells affected by the

pathogens wherein the interactions can be described as those of ligands and receptors. Basic concepts for the biochemical and biophysical characterization of such interactions are described (pages 517-521) as are the functions of ligands and receptors in infectious diseases (521-527). In a separate section, Keusch also describes some therapeutic implications of specific receptors acting as binding sites for ligands (pages 527-528); included among these are the ideas of generating and/or manipulating the ligands and/or receptors to block binding of the pathogen to cells. As described in Keusch, the ligand-receptor pairs to which these principles apply are not limited to the specific examples given, nor even to the broader group of pathogens and their target cells (page 517, second column). Therefore, Applicants submit that the skilled practitioner of the art would both appreciate that the present invention is directed to a broader group of ligand/receptor pairs than is described by way of example in the specification and would further be able envision a large number of embodiments based upon the general principles which those specifically-recited examples exemplify to one of skill in the art who had in his possession the teachings of the present invention and of Keusch or its equivalent.

Similarly, Applicants submit that Karlsson et al., attached as Exhibit J, provides further evidence that a skilled practitioner, reading the present application, would have recognized broad embodiments of the present invention. In the context of recognizing that a microbe must first specifically adhere to the target cell to cause pathogenesis, Karlsson et al. describe the manipulation of a number of different carbohydrates normally present on cell surfaces to which pathogens have specific receptors (Karlsson et al., *APMIS Suppl. 27*, 100: 71-83 (1992)). General properties underlying the interactions between polysaccharides and carbohydrate receptors of microbes are also presented along with a number of illustrative examples. The authors apply these general principles of microbial cell adhesion to "mop-up" pathogenic microbes, thereby diverting them from binding to target cells and also thereby preventing pathogenesis is described (page 81). This general technique, termed anti-adhesion therapy, relies upon the generation and manipulation of ligand/receptor pairs. Karllson et al. describe the technique as being applicable to rational drug

design (pages 81-82) even without detailed structural knowledge of the protein which specifically interacts with the receptor saccharides. Karllson et al. and references cited therein demonstrate the recognition by those of skill in a related art that ligand receptor pairs even quite dissimilar to those described by way of example in the specification can be routinely manipulated and modified. Applicants therefore submit that one of skill in the art would be able to apply these teachings to the present step of covalently linking a variety of receptor-type molecules to cell surfaces, and targeting those covalently linked molecules with recognized ligands to perform the present invention.

Finally, Applicants submit that Spear et al., presented as Exhibit K, provides evidence attesting to the well-developed state of the art regarding receptor-ligand pairs (Spear et al., in Heparin and Related Polysaccharides, pp. 341-353, eds. Lane et al., Plenum Press, NY (1992)). Specifically, Spear et al. summarizes the evidence for heparan sulfate moieties of proteoglycans acting as cell surface receptors for herpes simplex virus and describe the heparin-binding viral proteins which bind the proteoglycans which act as cell surface receptors (see Introduction, page 341). As Spear et al. provides both the cell surface receptors (see Table 1, page 343) for the binding of herpes simplex virus to cells and specific proteins, including glycoprotein B (page 346), glycoprotein C (pages 347-348) and both HSV-1 and HSV-2 (pages 348-349), which act as ligands, they provide yet another example of the types of ligand receptor pairs which would be recognized by those of skill in the art to be amenable to the practice of the invention.

Thus, the art, read in light of the specification, provides enablement for the genus of receptor-ligand pairs, for covalently linking the genus of receptors to cells, and for contacting the covalently linked receptor with its ligand(s) linked to the genus of bio-active molecules. In light of the substantial evidence of the skill in the art at the time this application was filed, Applicants respectfully assert that the Examiner's assertion of lack of enablement is rebutted. Thus, withdrawal of this rejection is believed to be merited an is respectfully requested.

Pursuant to the above remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of the application to issue.

A check in the amount of $110.00 and a Request for a One Month Extension of Time are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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Gwendolyn D. Spratt — Date: 8-24-01

Version with Markings to Show Changes Made

In the claims:

9. (Amended) A composition comprising a nucleic acid-polyethylenimine-avidin complex, wherein the polyethyleneimine is covalently linked to avidin.